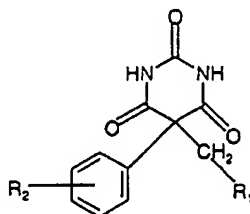




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(54) Title: PYRIMIDINE-2,4,6-TRIONES AS INHIBITORS OF MATRIX METALLOPROTEINASES



(I)

(57) Abstract

The novel compounds of formula (I) wherein R₁ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, aryloxy or alkylalkoxy, and R₂ is aryloxy; pharmaceutically acceptable salts of an acidic compound of formula (I), and prodrugs thereof can be used in the treatment or control of cancer associated with overexpression of gelatinase-A and/or gelatinase-B, particularly skin cancer, breast cancer, prostate cancer, colon cancer, lung cancer, and gastric cancer, and are also useful for other diseases associated with unregulated degradation of extracellular matrix, including rheumatoid arthritis, osteoarthritis, multiple sclerosis, corneal ulceration, periodontal disease and the like.

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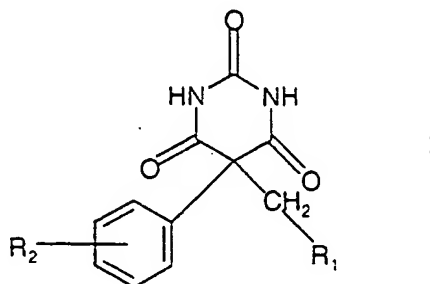
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PYRIMIDINE-2,4,6-TRIONES AS INHIBITORS OF MATRIX METALLOPROTEINASES

The invention relates to compounds of formula I



5

wherein

R₁ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, aryloxy or alkylalkoxy, and

10

R₂ is aryloxy;

pharmaceutically acceptable salts of an acidic compound of formula I, and prodrugs thereof.

The compounds of the invention are matrix metalloprotease inhibitors useful for
15 treating or controlling cancer associated with overexpression of gelatinase-A and/or gelatinase-B, particularly skin cancer, breast cancer, prostate cancer, colon cancer, lung cancer, and gastric cancer. The compounds of the invention are also useful for other diseases associated with unregulated degradation of extracellular matrix, including rheumatoid arthritis, osteoarthritis, multiple sclerosis, corneal ulceration, periodontal
20 disease and the like.

A prodrug is a compound that may be converted under physiological conditions to a compound of formula I or a pharmaceutically acceptable salt thereof. Preferably, a prodrug is an acyl or alkylmethyl ether derivative of a compound of formula I or a
25 pharmaceutically acceptable salt thereof.

As used herein, the term "alkyl" means a straight or branched-chain alkyl group containing a maximum of 13, preferably a maximum of 7, carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, t-butyl, and pentyl, hexyl and the like.

5 The term "substituted alkyl" means alkyl which is substituted by one or more substituents, examples of which are hydroxy, halogen, and aryl.

10 The term "alkenyl" means a straight or branched chain hydrocarbon group containing a maximum of 13, preferably a maximum of 7, and at least 2, carbon atoms, and at least one double bond, such as ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like.

The term "substituted alkenyl" means alkenyl which is substituted by one or more substituents, examples of which are hydroxy, halogen, and aryl.

15 The term "alkynyl" means a straight or branched chain hydrocarbon group containing a maximum of 13, preferably a maximum of 7, and at least 2, carbon atoms, and at least one triple bond.

20 The term "substituted alkynyl" means alkynyl which is substituted by one or more substituents, examples of which are hydroxy, halogen, and aryl.

The term "alkoxy" means a straight or branched-chain alkoxy group containing a maximum of 11, preferably a maximum of 5, carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy and the like.

25

The term "substituted alkoxy" means alkoxy which is substituted by one or more substituents, examples of which are hydroxy, halogen and aryl.

30 The term alkylalkoxy means a combination of an alkyl or substituted alkyl group and an alkoxy or substituted alkoxy group.

35 The term "aryl", alone or in combination, means an aromatic carbocyclic ring or a heterocyclic ring, which is unsubstituted or substituted by one or more, preferably one to three, substituents, examples of which are alkyl, hydroxy, alkoxy, and halogen. Examples of aromatic carbocyclic rings are phenyl and naphthyl. Examples of aromatic heterocyclic rings are pyridino, pyrrolo, thienyl, pyrazalo, imidazalo, thiazalo, oxazalo, triazalo, teatrazalo, oxadiazalo, thiadiazolo, benzofuryl, benzothienyl, benzinidazalo, benzotriazalo,

quinololyl, isoquinolyl, and indolyl. Most preferably, aryl is an unsubstituted phenyl group or phenyl group having one or more, preferably one to three, substituents, examples of which are halogen, alkyl, hydroxy, alkoxy, and halogen.

5 The term "halogen" means fluorine, chlorine, bromine, or iodine.

 The term "acyl" means a group derived from an alkanolic acid, for example, acetyl, propionyl or butyryl, or from an aromatic carboxylic acid for example, benzoyl. Examples of substituents on alkanolic acid includes one or more of the following: hydroxy, alkoxy,
10 amino, halogen, thioalkyl, carboxy, carboxylic acid derivative or alkyl sulphonyl and the like. Examples of substituents on aromatic carboxylic acid include one or more of the following: halogen, alkyl, hydroxy, benzyloxy, alkoxy, haloalkyl, nitro, amino, cyano and the like.

15 Preferably, R_1 is hydrogen, alkyl, substituted alkyl, or substituted alkoxy. More preferably, R_1 is hydrogen, alkyl containing a maximum of 7 carbon atoms, substituted alkyl containing a maximum of 7 carbon atoms (preferably hydroxymethyl) or substituted alkoxy containing a maximum of 5 carbon atoms (preferably benzyloxy).

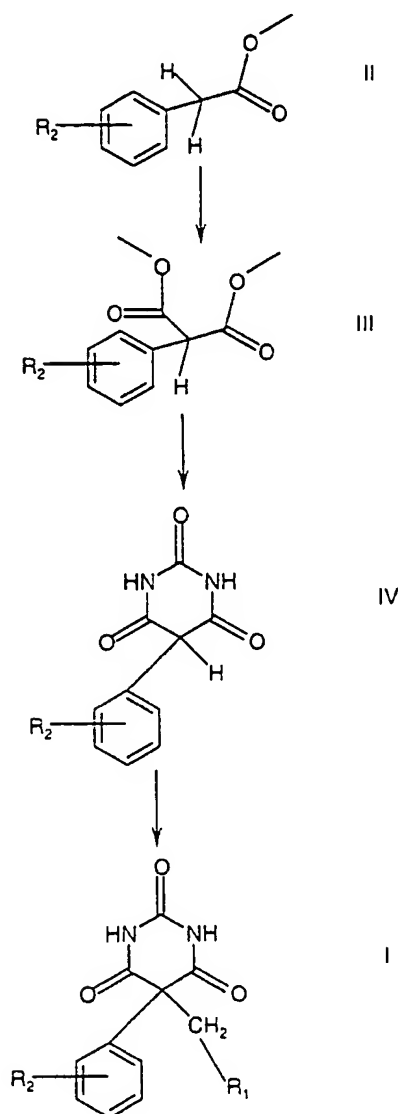
20 Preferably, R_2 is in the para position. More preferably, R_2 is phenoxy.

 Most preferred are the compounds, 5-methyl-5-(4-phenoxyphenyl) pyrimidine-2,4,6-trione, 5-hexyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione, 5-benzyloxymethyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione, and 5-(2-hydroxyethyl)-5-(4-
25 phenoxyphenyl)pyrimidine-2,4,6-trione.

 The compounds of formula I may be prepared by the following Schemes I-II.

The compounds of formula I are prepared by the following Scheme I.

SCHEME I



Compounds of formula III are prepared by treatment of compounds of formula II
5 with a strong base, such as sodium hydride, lithium diisopropylamide, or lithium
bis(trimethylsilyl)amide, in an aprotic solvent such as tetrahydrofuran (THF). The
resultant anion is then reacted with dimethylcarbonate or methyl chloroformate at
temperatures ranging from room temperature to reflux to form a compound of formula
III.

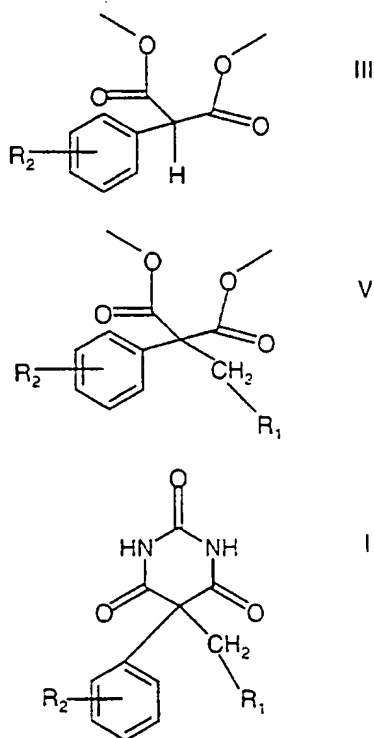
The compounds of formula IV are prepared by reacting a compound of formula III with urea in a basic solution, such as sodium methoxide in methanol, at reflux.

The compounds of formula I are prepared by reacting a compound of formula IV
5 with a strong base, such as sodium hydride, lithium diisopropylamide, lithium
bis(trimethylsilyl)amide, in an aprotic solvent, such as THF, to form an anion. The anion
is then treated with alkyl halide, such as methyl iodide, hexyl bromide, allyl bromide, or
benzyl chloromethyl ether, at temperatures varying from room temperature to reflux. N-
substituted-2,4,6-triones are then removed by chromatography to provide the desired
10 compound of formula I.

The compounds of formula II are known or can prepared by known methods.

The compounds of formula I can also be prepared as described in Scheme II.

SCHEME II



Compounds of formula V are prepared by reacting a compound formula III with a strong base such as sodium hydride, lithium diisopropylamide, lithium bis(trimethyl-silyl)amide, in an aprotic solvent such as THF. The resulting anion is then treated with an alkyl halide, such as methyl iodide, hexyl bromide, allyl bromide, or benzyl chloromethyl ether, at temperatures varying from room temperature to reflux.

In the case of a compound of formula V wherein R_1 is hydroxymethyl, compounds of formula V are also prepared by reacting a compound formula III with a strong base such as sodium hydride, lithium diisopropylamide, lithium bis(trimethyl-silyl)amide, in an aprotic solvent such as THF. The resulting anion is then treated with ethylene oxide. Alternatively, in the case of a compound of formula V wherein R_1 is hydroxymethyl, compounds of formula V are also prepared by carrying out oxidative cleavage of the compound of formula III, dimethyl 2-(2-propenyl)-2-(4-phenoxy-phenyl)malonate, with ozone and reducing the resultant ozonide with a phosphine or a thiol to give the aldehyde which is then reduced to the alcohol, using a reducing agent such as sodium borohydride.

Compounds of formula I are prepared by heating compounds of formula V with urea in the presence of $Mg(OCH_3)_2$ as a paste at 80 - 100° C for a period of time necessary to complete the reaction.

If desired, an acidic compound of formula I can be converted into a pharmaceutically acceptable salt with a base in a known manner. Suitable salts are those derived not only from inorganic bases, for example, sodium, potassium or calcium salts, but also from organic bases such as ethylenediamine, monoethanolamine or diethanolamine.

Prodrugs are made, for example, by reacting activated acids with a compound of formula I by known methods, or by reacting halomethylalkyl ether with a compound of formula I by known methods.

The compounds of formula I and their pharmaceutically acceptable salts and prodrugs inhibit matrix metalloprotease and so are useful for treating or controlling cancer associated with overexpression of gelatinase-A and/or gelatinase-B, particularly skin cancer, breast cancer, prostate cancer, colon cancer, lung cancer, and gastric cancer. The compounds of the invention are also useful for other diseases associated with unregulated

degradation of extracellular matrix, including rheumatoid arthritis, osteoarthritis, multiple sclerosis, corneal ulceration, periodontal disease and the like.

Human 72 kDa gelatinase was purified from the conditioned media of fetal lung
5 fibroblasts according to known methods. The enzyme was stored in the pro-form at -80°C
and activated prior to use by treatment with 1 mM aminophenyl mercuriacetate (APMA)
for 1 hour at 37°C , then dialyzed against reaction buffer before use. Human neutrophil
gelatinase (95 kDa gelatinase) was purified from conditioned media of NSO-cells according
to known methods. This enzyme was likewise stored in the zymogen form at -80°C . It was
10 activated by treatment with trypsin ($5\text{ }\mu\text{g/mL}$) for 1 hour at 37°C , followed by addition of
bovine pancreatic trypsin inhibitor to $50\text{ }\mu\text{g/mL}$. Human matrilysin was obtained from a
bacterial expression system as a ubiquitin fusion construct Welch; A. R., Holman, C. M.,
Browner, M. F., Gehring, M. R., Kan, C.-C., & Van Wart, H. E. (1995) *Arch. Biochem.*
Biophys. 324, 59-64. The mature form of matrilysin was purified following activation with
15 1 mM APMA (1 hour, 37°C) and the active enzyme stored at -80°C . The catalytic domain
of human collagenase-3 was obtained in a manner analogous to that for matrilysin. The
final form of collagenase-3 used for these studies consisted of the residues Tyr₁₀₄ - Asn₂₇₄
from the full length collagenase sequence. The catalytic domain of human stromelysin-1
was produced via *E. coli* expression and purification according to known methods; the
20 activated, catalytic domain was stored at -80°C .

The assay methods utilized the fluorogenic substrate: Dnp-Pro-Cha-Gly-Cys(Me)-
His-Ala-Lys(NMA)-NH₂. (Dnp = dinitro phenyl; Cha = cyclohexylalanine; Cys(Me) = S-
methyl cysteine, Lys(NMA) = N^ε-methyl-anthranoyl-L-lysine). Stock solutions were
25 prepared in DMSO. Stock solutions of compounds of formula I (inhibitor) were also
prepared in DMSO. All reactions had a net final DMSO level of 5% (v/v) in the indicated
buffers for the enzymes.

For gelatinase-A and gelatinase-B, the buffer was pH 7.5, 50 mM TrisHCl, 200 mM
30 NaCl, 5 mM CaCl₂, 20 μM ZnCl₂, 0.05% (wt/v) Brij-35. For matrilysin and the catalytic
domain of collagenase-3, the buffer composition was pH 7.5, 50 mM Hepes, 200 mM NaCl,
5 mM CaCl₂, 20 μM ZnCl₂, 0.05% (wt/v) Brij-35. The final substrate concentration in all
cases 10 μM . The approximate concentrations for the enzymes were: gelatinase-A, 0.8 nM;
gelatinase-B, 0.5 nM; collagenase-3, 0.4 nM; matrilysin, 10 nM. To perform the peptide
35 cleavage assay, the vessel containing buffer and compound of formula I were pre-
equilibrated at 37°C , then the reaction initiated by successive addition of concentrated

stocks of enzyme and substrate, and incubation at 37°C was continued. At successive time points between 30 and 120 minutes, 50 µL aliquots of the assays were pulled and the enzymatic reaction stopped by addition to 150 µL of 30 mM EDTA (pH 7.4) in the well of a black, flat bottom microtiter plate. The extent of substrate conversion was determined by reading the fluorescence of the stopped reactions (excitation wavelength: 355 nm; emission wavelength: 460 nm). Positive controls were run in the absence of inhibitor; negative controls had no enzyme and showed negligible spontaneous cleavage.

Plots of the fluorescence vs time (30 - 120 min) were linear; comparison to standards showed the substrate conversion was <20% in all instances. A rate at each inhibitor concentration was obtained from a linear least squares fit to the fluorescence time course. The percent inhibition at inhibitor concentration [I] was calculated as:

$$\%inh[I] = 100(1 - rate[I]/ratePC)$$

where

$\%inh[I]$ = percent inhibition at inhibitor concentration [I]

rate[I] = rate at inhibitor concentration [I]

ratePC = rate of positive control

The IC₅₀ for the inhibitor was then obtained by fitting the concentration dependence of the $\%inh[I]$ to the simple binding isotherm:

$$\%inh[I] = 100([I]/(IC_{50} + [I]))$$

Measurements for stromelysin-1: the catalytic domain of stromelysin-1 was tested using the same substrate but with a modified protocol. The assay buffer was pH 6.5 50 mM Mes, 2.5 mM EDTA, 5 mM CaCl₂, and 0.05% (wt/v) Brij-35. The substrate concentration was 10 µM and the enzyme concentration was 10 nM. Reactions were performed at ambient temperature. Appropriate portions of buffer, substrate, and inhibitor were combined in the well of a black, flat bottom microtiter plate. The reaction was started by addition of an aliquot of enzyme stock and the generated fluorescence was read directly after 60 minutes. Positive controls were run in the absence of inhibitor. Negative controls lacked enzyme and showed a finite increase during the course of the assay; to correct the enzymatic reactions, this background fluorescence was subtracted from the values for the positive control and the inhibited reactions. The $\%inh[I]$ was calculated as:

$$\%inh[I] = 100(1 - Fluor[I]/FluorPC)$$

where Fluor[I] = corrected fluorescence at 60 minutes observed for inhibitor concentration [I]

FluorPC = corrected fluorescence at 60 minutes observed for the positive control

- 5 The IC_{50} for the inhibitor was then obtained by fitting the %inh[I] to the single site binding isotherm indicated above.

The IC_{50} are provided in the Table below for compounds of formula I.

Compound	Strom-1	Matr	Coll-3	GelA	GelB
A	2 μ M	>50 μ M	65nM	80nM	52nM
B	2 μ M	>50 μ M	78nM	67nM	50nM
C	930nM	>50 μ M	47nM	26nM	23nM
D	-----	-----	-----	59nM	118nM

- 10 A = 5-methyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione.
 B = 5-hexyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione.
 C = 5-benzyloxymethyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione.
 D = 5-(2-hydroxyethyl)-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione.

- 15 The compounds of formula I and their salts and prodrugs can be used as medicaments, for example, in the form of pharmaceutical preparations, which can be administered orally, for example, in the form of tablets, coated tablets, dragees, hard or soft gelatin capsules, solutions, emulsions or suspensions. They can also be administered rectally, for example, in the form of suppositories or parenterally, for example in the form
 20 of injection solutions.

- For the manufacture of pharmaceutical preparations these compounds can be formulated with therapeutically inert, inorganic or organic carriers. Lactose, maize starch or derivatives thereof, talc, stearic acid or its salts can be used as such carriers for tablets,
 25 coated tablets, dragees and hard gelatin capsules. Suitable carriers for soft gelatin capsules are vegetable oils, waxes, fats, semi-solid or liquid polyols. Depending on the nature of the active substance no carriers are, however, generally required in the case of soft gelatin capsules. Suitable carriers for the manufacture of solutions and syrups are water, polyols, saccharose, invert sugars, and glucose. Suitable carriers for injection solutions are water,

alcohols, polyols, glycerine and vegetable oils. Suitable carriers for suppositories are natural or hardened oils, waxes, fats and semi-liquid polyols.

The pharmaceutical preparations can also contain preserving agents, solubilizing
5 agents, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances.

The compounds of formula I and their aforementioned salts and prodrugs can be
10 used in the treatment or control of cancer associated with overexpression of gelatinase-A and/or gelatinase-B, particularly skin cancer, breast cancer, prostate cancer, colon cancer, lung cancer, and gastric cancer. The compounds of the invention are also useful for other diseases associated with unregulated degradation of extracellular matrix, including
15 rheumatoid arthritis, osteoarthritis, multiple sclerosis, corneal ulceration, periodontal disease and the like. The dosage can vary within wide limits and will be adjusted to the individual requirements of each particular case. In general, in the case of oral or parenteral administration to adult humans, a daily dosage of about 10 mg to 1000 mg, and preferably 100 mg to 500 mg, should be appropriate, although the upper limit may be exceeded when this is found to be expedient. The daily dose can be administered as a single dose or in
20 divided doses, or for parenteral administration, it may be given as continuous infusion.

The following examples illustrate, without limitation, the present invention. As used herein, THF means tetrahydrofuran and EtOAc means ethyl acetate.

25

Example 1

To a suspension of NaH (1.02 g of 60% NaH in mineral oil washed with hexanes, 0.61 g, 25.6 mmol) in dry THF (30 mL) was added methyl (4-phenoxyphenyl)acetate (2.7 g, 11.1 mmol) in dry THF (10 mL). The resulting mixture was stirred at room temperature for
30 30 minutes and then dimethylcarbonate (4.0 g, 3.75 mL, 44.4 mmol) was added. The reaction mixture was heated to reflux overnight and then cooled to room temperature, quenched with 1N HCl (60 mL), and extracted with ether (2x100 mL). The combined organic extracts were washed with water, then brine, dried (Na₂SO₄), concentrated, and purified using HPLC (porasil) eluted with 15% EtOAc/hexanes to give 2.56 g of dimethyl
35 2-(4-phenoxyphenyl)malonate as a white solid: ¹H NMR (200 MHz, CDCl₃) δ 7.39-6.92 (9H, m), 4.65 (1H, s), 3.75 (6H, s).

Example 2

To a NaOCH₃ solution (prepared by allowing 0.23 g of Na metal to react with 7.2 mL dry CH₃OH) was added dimethyl 2-(4-phenoxyphenyl)malonate (1.0 g, 3.33 mmol) followed by urea (0.4 g, 6.66 mmol). The resulting white reaction mixture was refluxed for 24 hours and then cooled to 0 °C and acidified with 3N HCl. The white solids were filtered and washed with water and dried to give 900 mg of crude product. This was further purified by trituration with EtOAc/hexanes (1:1) to afford 5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione as a white powder (830 mg): ¹H NMR (400 MHz, CDCl₃) 3:2 keto/enol form δ 11.38 (2xNH keto form, s), 10.58 (2xNH enol form, s), 7.46-6.91(9H, m), 4.85 (H-5, s); HRMS Calcd for C₁₆H₁₂N₂O₄ 296.0796; Found 296.0806.

Example 3

Carried out under an inert atmosphere:

To a suspension of NaH (16.21 g of 60% in mineral oil, 9.72 mg, 0.405 mmol) in dry THF was added 5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione (100 mg, 0.34 mmol). After the mixture stirred at room temperature for 30 minutes, methyl iodide (48.2 mg, 0.34 mmol) was added. The reaction was stirred at room temperature for 3 hours and then additional NaH (24 mg of 60% in mineral oil, 14 mg, 0.60 mmol) was added followed by methyl iodide (96.4 mg, 0.86 mmol). This reaction mixture was stirred at room temperature for 2 hours and then refluxed overnight. The reaction solution was diluted with EtOAc and then quenched with 1N HCl. The organic layer was separated washed with water, brine, dried (Na₂SO₄), concentrated, and then purified by chromatography on a Chromatotron using a silica gel plate (1000 micron) with 30% EtOAc/ hexanes and then 50% EtOAc/hexanes and finally EtOAc to afford 1,3-di-N-methyl-5-methyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione (7.3 mg) and 1-N-methyl-5-methyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione (10.0 mg) and then 5-methyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione (27 mg) in order of elution.

Spectra for 5-methyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione: ¹H NMR (200 MHz, CD₃OD) δ 7.37-6.95 (9H, m), 1.77 (3H, s); HRMS Calcd for C₁₇H₁₄N₂O₄ 310.0954; Found 310.0963.

Spectra for 1-N-methyl-5-methyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione:

^1H NMR (200 MHz, CDCl_3) δ 8.38 (1NH, s), 7.39-6.92 (9H, m), 3.31 (3H, s), 1.86 (3H, s); HRMS Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_4$ 324.1110; Found 324.1116.

- 5 Spectra for 1,3-di-N-methyl-5-methyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione: ^1H NMR (200 MHz, CDCl_3) δ 7.38-6.91 (9H, m), 3.34 (6H, s), 1.85 (3H, s); HRMS Calcd for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_4$ 338.1267; Found 338.1267.

Example 4

10 Step 1:

Carried out under an inert atmosphere:

- To a suspension of NaH (144 mg of 60% in mineral oil washed with hexanes, 86.4 mg, 3.6 mmol) in dry THF (20 mL) was carefully added dimethyl 2-(4-phenoxyphenyl)malonate (900 mg, 3.0 mmol). The resulting mixture was stirred
15 at room temperature for 1 hour and then 1-iodohexane (1.27 g, 0.89 mL, 6.0 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour and then heated to reflux overnight. The reaction was cooled to room temperature and quenched with 1N HCl (20 mL) and extracted with ether (2x40 mL). The combined organic extracts were washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$,
20 water, then brine, dried (Na_2SO_4), concentrated, and purified by chromatography using a Chromatotron with a silica gel plate (4000 micron) eluted with 13% EtOAc/hexanes to give 950 mg of dimethyl 2-(4-phenoxyphenyl)-2-n-hexylmalonate as a viscous oil. ^1H NMR (200 MHz, CDCl_3) δ 7.39-6.92 (9H, m), 3.75 (6H, s), 2.10 (2H, t), 1.29 (8H, m), 0.87 (3H, t).

25

Step 2:

- $\text{Mg}(\text{OCH}_3)_2$ was prepared as follows: To a 25 mL round-bottom flask under argon was added Mg turnings (90 mg, 3.70 mmol), dry CH_3OH (2 mL), 2 drops of CCl_4 and a catalytic amount of Mg powder. An exothermic reaction took place
30 and hydrogen gas evolution was observed. After the initial exothermic reaction subsided, the reaction mixture was heated to reflux for 1 hour and then cooled to room temperature. Dimethyl 2-(4-phenoxyphenyl)-2-n-hexylmalonate (500 mg, 1.30 mmol) and urea (162 mg, 2.70 mmol) were added to the $\text{Mg}(\text{OCH}_3)_2$. The reaction mixture was heated at 85-90°C for 1 hour and then excess CH_3OH was
35 distilled off until a fluid-paste was obtained and this paste was then heated at 85-90°C overnight. The reaction was cooled to room temperature, diluted with

EtOAc, and washed with 1N HCl. The acidic aqueous layer was re-extracted with EtOAc. The combined EtOAc extracts were washed with water, brine, dried (MgSO_4), and concentrated. The resulting oil was purified with HPLC (porasil) using 30% EtOAc/hexanes as eluent to afford 330 mg of 5-n-hexyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione as a white foam: ^1H NMR (400 MHz DMSO- d_6) δ 11.71 (2NH, s), 7.42-6.99 (9H, m), 2.22 (2H, t), 1.24 (8H, m), 0.85 (3H, t); HRMS Calcd for $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4$ 380.1736; Found 380.1740.

Example 5

10 Step 1:

Carried out under an inert atmosphere.

To a suspension of NaH (0.37 g of 60% in mineral oil washed with hexanes, 0.22 g, 9.2 mmol) in dry THF (30 mL) was carefully added dimethyl 2-(4-phenoxyphenyl)malonate (2.5 g, 8.33 mmol). The resulting mixture was stirred
15 at room temperature for 30 minutes and then benzyl chloromethyl ether (1.43 g, 1.27 mL, 9.16 mmol) was added. The reaction mixture was stirred at room temperature overnight and quenched with sat. NH_4Cl and then extracted with ether (100 mL). The ether extract was dried (MgSO_4), and concentrated to give 4.0 g of viscous oil. This was purified using HPLC (porasil) eluted with 15%
20 EtOAc/hexanes to give 2.1 g of dimethyl 2-benzyloxymethyl-2-(4-phenoxyphenyl)malonate as a viscous oil: ^1H NMR (200 MHz, CDCl_3) δ 7.48-6.95 (14H, m), 4.55 (2H, s), 4.20 (2H, s), 3.75 (6H, s).

Step 2:

25 $\text{Mg}(\text{OCH}_3)_2$ was prepared as described in Example 4 Step 2 from: Mg (116 mg, 4.76 mmol), dry CH_3OH (3.0 mL), 1 drop of CCl_4 , catalytic amount of Mg powder. To this was added dimethyl 2-benzyloxymethyl-2-(4-phenoxyphenyl)malonate (700.0 mg, 1.67 mmol), urea (208.0 mg, 3.47 mmol) and the mixture heated to reflux and then excess CH_3OH distilled off until a paste was obtained.
30 The resulting paste was heated at 85-90°C overnight. Workup as described in Example 4 gave, after concentration, a viscous oil (0.75 g) which was chromatographed using a Chromatotron with a silica gel plate (4000 micron) and eluted with 40% EtOAc/hexanes to give 180 mg of 5-benzyloxymethyl-5-(4-phenoxyphenyl)pyrimidine-2,4,6-trione as a white solid: ^1H NMR (400 MHz, DMSO- d_6) δ 8.01 (2NH, s), 7.38-6.94 (15H, m), 4.58 (2H, s), 4.27 (2H, s); HRMS
35 Calcd for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_5$ 416.1372; Found 416.1383.

Example 6**Step 1:**

A solution of dimethyl 2-(4-phenoxyphenyl)malonate (2.56 g, 8.54 mmol) in dry THF (50 mL) was cooled to -78°C and then lithium diisopropylamide (4.7 mL of a 2M solution in THF, 9.8 mmol) was added. The reaction was stirred at -78°C for 1 hour and then allyl bromide (11.4 mg, 9.4 mmol) was added. The reaction was stirred at -78°C for 3 hours and then allowed to warm to room temperature and heated in a 75°C oil bath until the reaction was shown to be complete by TLC. The reaction was cooled to room temperature and quenched with 1N HCl. Extraction with ether and drying of the ether extracts (MgSO_4) gave crude product. Purification by filtration through silica gel 60 (70-230 mesh) using EtOAc, followed by HPLC (porasil) using 11% EtOAc/hexanes gave 1.8 g of dimethyl 2-(2-propenyl)-2-(4-phenoxyphenyl)malonate as a viscous oil: ^1H NMR (200 MHz, CDCl_3) δ 7.4-6.85 (9H, m), 5.75 (1H, m), 5.05 (2H, m), 3.75 (6H, s), 3.1 (2H, d).

Step 2:

A solution of dimethyl 2-(2-propenyl)-2-(4-phenoxyphenyl)malonate (1.8 g, 5.3 mmol) in CH_2Cl_2 (200 mL) was cooled to -70°C and then O_3 bubbled through until a blue color persisted. The blue solution was degassed with argon and while still at -70°C was treated with Ph_3P (4.0 g, 15.2 mmol) and allowed to warm slowly to room temperature. Concentration, followed by purification by HPLC (porasil) using 20% EtOAc/hexanes gave 1.66 g of the aldehyde as an oil. This was dissolved in CH_3OH (50 mL) and NaBH_4 (0.184g, 4.85 mmol) was added and the reaction stirred at room temperature 30 minutes. Following concentration, the residue was dissolved in EtOAc and washed with water, brine, and then dried (MgSO_4), and concentrated to give 1.55 g of a mixture of dimethyl 2-(2-hydroxyethyl)-2-(4-phenoxyphenyl)malonate and its derived lactone.

Step 3:

$\text{Mg}(\text{OCH}_3)_2$ was prepared as described in Example 4 Step 2 from: Mg (116 mg, 4.76 mmol), 3 mL of CH_3OH , 1 drop of CCl_4 , and a catalytic amount of Mg powder. To this was added the above mixture of dimethyl 2-(2-hydroxyethyl)-2-(4-phenoxyphenyl)malonate and its derived lactone (521 mg, 1.67 mmol) and urea (228 mg, 3.47 mmol) and the mixture heated to reflux and then excess CH_3OH distilled off until a paste was obtained. The resultant paste was heated at

85-90 °C for 8 hours and then cooled to room temperature. The reaction was partitioned between EtOAc and 10 mL 1N HCl. The EtOAc layer was separated, dried (Na₂SO₄), and concentrated to give 600 mg of a crude product.

Chromatography using a Chromatotron with a silica gel plate (2000 micron)

- 5 eluted with EtOAc gave 120 mg of pure 5-(2-hydroxyethyl)-5-(4-phenoxy-phenyl)pyrimidine-2,4,6-trione as a white solid: IR (KBr) 3214, 3100, 1765(sh), 1705 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ 11.48 (2H, br s, N-H), 7.45-6.95 (9H, m), 4.85 (1H, t, OH), 3.50 (2H, m), 2.50 (2H, m); HRMS Calcd for C₁₈H₁₆N₂O₅ 340.1059, Found 340.1055.

Example 7TABLET FORMULATION

Item	Ingredients	mg/Tablet					
		5mg	25mg	100mg	250mg	500mg	750mg
KERNEL:							
1	Compound of formula I	5.0	25.0	100.0	250.0	500.0	750.0
2	Anhydrous Lactose	104.4	84.4	36.8	23.5	47.0	70.5
3	Croscarmellose Sodium	6.0	6.0	7.5	15.0	30.0	45.0
4	Povidone K30	3.6	3.6	4.5	9.0	18.0	27.0
5	Magnesium Stearate	1.0	1.0	1.2	2.5	5.0	7.5
<u>Kernel Weight</u>		120	120	150	300	600	900
FILM COAT:							
6	Hydroxypropyl Methyl-cellulose 6 cps-2910	1.6	1.6	2.0	4.0	8.0	12.0
7	Talc	1.2	1.2	1.5	3.0	6.0	9.0
8	Titanium Dioxide	1.2	1.2	1.5	3.0	6.0	9.0
<u>Total Tablet Weight</u>		124	124	155	310	620	930

5

Manufacturing Procedure:

1. Mix Items 1, 2 and 3 in a suitable mixer for 15 minutes.
2. Granulate the powder mix from Step 1 with 15% Povidone K30 Solution (Item 4).
3. Dry the granulation from Step 2 at 50°C.
4. Pass the granulation from Step 3 through a suitable milling equipment.
5. Add the Item 5 to the milled granulation Step 4 and mix for 5 minutes.
6. Compress the granulation from Step 5 on a suitable press.
7. Using a suitable air spray system, coat the kernels from Step 6 with a Film Coat Suspension containing Hydroxypropyl Methylcellulose 6 cps-2910, Talc and Titanium Dioxide.

15

Example 8

CAPSULE FORMULATION

5

Item	Ingredients	mg/Capsule				
		5mg	25mg	100mg	250mg	500mg
1	Compound of formula I	5	25	100	250	500
2	Hydrous Lactose	159	123	148	50	75
3	Corn Starch	25	35	40	35	70
4	Talc	10	15	10	12	24
5	Magnesium Stearate	1	2	2	3	6
<u>Total Fill Weight</u>		200	200	300	350	675

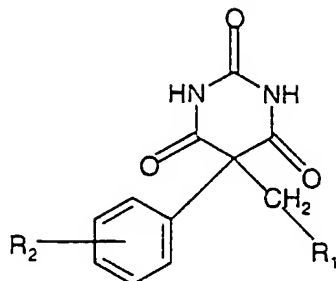
Manufacturing Procedure:

10

1. Mix Items 1, 2 and 3 in a suitable mixer for 15 minutes.
2. Add Items 4 & 5 and mix for 3 minutes.
3. Fill the powder mix from Step 2 into a suitable capsule.

CLAIMS

1. Compounds of formula I



5

wherein

R₁ is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkoxy, alkynyl, substituted alkynyl, alkoxy, substituted alkoxy, aryloxy or alkylalkoxy; and

10

R₂ is aryloxy;

pharmaceutically acceptable salts of an acidic compound of formula I, and prodrugs thereof.

15

2. The compounds of Claim 1, wherein R₂ is in the para position.

3. The compounds of Claim 2, wherein R₂ is phenoxy.

4. The compounds of Claim 3, wherein R₁ is hydrogen, alkyl substituted alkyl, or alkoxy.

20

5. The compounds of Claim 3, wherein R₁ is substituted alkoxy or alkylalkoxy.

6. The compounds of Claim 3, wherein R₁ is benzyloxy.

25

7. 5-Methyl-5-(4-phenoxyphenyl) pyrimidine-2,4,6-trione.

8. 5-Hexyl-5-(4-phenoxyphenyl) pyrimidine-2,4,6-trione.

9. 5-Benzylloxymethyl-5-(4-phenoxy-phenyl)pyrimidine-2,4,6-trione.
- 5 10. 5-(2-Hydroxyethyl)-5-(4-phenoxy-phenyl)pyrimidine-2,4,6-trione.
11. A compound as defined in any one of claims 1-10 for use as a medicament.
- 10 12. A pharmaceutical composition comprising a compound as defined in any one of claims 1-10, and a pharmaceutically acceptable carrier.
13. The use of a compound as defined in any one of claims 1-10 in the
15 manufacture of a medicament containing such compound for the treatment or control of skin cancer, breast cancer, prostate cancer, colon cancer, lung cancer, gastric cancer, rheumatoid arthritis, osteoarthritis, multiple sclerosis, corneal ulceration, or periodontal disease.
- 20 14. The novel compounds, compositions and use as described hereinbefore, especially with reference to the Examples.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 00/01016

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/62 A61K31/515 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 58925 A (BOEHRINGER MANNHEIM G.M.B.H., GERMANY) 30 December 1998 (1998-12-30) claim 1 page 2, line 14 - line 15 page 23, line 5 - line 6 ---	1-13
A	WO 97 23465 A (BOEHRINGER MANNHEIM GMBH, GERMANY) 3 July 1997 (1997-07-03) claim 1 page 2, line 8 - line 9 ---	1-13
A	WO 98 58915 A (BOEHRINGER MANNHEIM G.M.B.H., GERMANY) 30 December 1998 (1998-12-30) claim 1 page 2, line 13 - line 15 -----	1-13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

23 May 2000

Date of mailing of the international search report

05. 06. 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/01016

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-6 (part), 11-13 (part); 14
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Claims Nos.: 1-6 (part), 11-13 (part); 14

Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The functional term "prodrug" does not enable the skilled person to determine which technical features are necessary to perform the stated function. It is thus unclear which specific compounds fall within the scope of said claim.

The term "as described hereinbefore" used in claim 14 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT). The term "new" introduces further unclarity to claim 14, since it could be interpreted as being either a qualitative or technical feature.

The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to claims 1 - 13 in so far as they refer to compounds of formula I and pharmaceutically acceptable salts thereof, and compositions and uses thereof.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/01016

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9858925 A	30-12-1998	AU 8539198 A EP 0989982 A HR 980340 A	04-01-1999 05-04-2000 28-02-1999
WO 9723465 A	03-07-1997	DE 19548624 A AU 1303697 A BR 9612232 A CA 2240845 A CN 1209123 A CZ 9801968 A EP 0869947 A HU 9901065 A NO 982901 A PL 327466 A ZA 9610765 A	26-06-1997 17-07-1997 13-07-1999 03-07-1997 24-02-1999 16-09-1998 14-10-1998 28-09-1999 24-08-1998 07-12-1998 17-07-1998
WO 9858915 A	30-12-1998	DE 19726427 A AU 8627898 A EP 0991626 A	24-12-1998 04-01-1999 12-04-2000